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EXAMINER

GAKH, YELENA G

ART UNIT PAPER NUMBER

1743

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

08/786,988

Applicant(s)

LITTLE ET AL.

Examiner

Yelena G. Gakh, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 09/18/03.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6,9-34,40-51,54-61,63-72,78 and 82-94 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6,9-34,40-51,54-61,63-72,78 and 82-94 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

1. RCE filed on 09/18/03 is acknowledged. Claims 1-6, 9-34, 40-51, 54-61, 63-72, 78 and 82-94 are pending in the application.

#### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 43-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims recite that the fluid comprises a solvent and a matrix material with no recitation of the analyte. There is no way for anyone of ordinary skill in the art to obtain reproducible MALDI mass spectra for the spots, which contain only matrix, since the matrix material does not reach a mass spectrometer detector in the MALDI experiment.

#### *Claim Rejections - 35 USC § 102*

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. **Claims 1-4, 6, 9-10, 14-15, 25-28 and 30** are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (JMS Letters).

Zhang teaches a method and an apparatus for dispensing a target material on a multi-well sample holder (substrate) (Fig. 1, page 1769, line 6-8). The method comprises the steps of

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providing a packed capillary (i.e. vesicle) having an interior chamber containing a fluid, disposing the vesicle adjacent a first location on the surface of the substrate and ejecting a defined and controlled ~5 nL volume of the fluid, while evaporating the solvent forms a spot of the sample of less than 0.3 mm<sup>2</sup>. MALDI-MS analysis is performed directly from the spot. The chamber is rinsed with a washing solution (Figure 1, page 1768, right column). It is absolutely clear from Figure 1 and its caption that the vesicle is moved from spot to spot to repeat these steps for each location (each well) of the multi-well holder, with ~ 5 nL of the sample fraction deposited in each spot. The accuracy of the volume is given exactly with the same precision as the one disclosed in the specification of the instant application: "into each well was dispensed 20 droplets (~ 5 nL) of 3-HPA matrix solution" (page 26, the last paragraph). No contacting of the vesicle with the substrate for disposing the liquid is indicated in the paper.

Reproducibility of the MALDI spectra obtained directly from the spots is intrinsic to the substrate having the same wells, the same volumes of the sample placed in the wells (~ 5 nL), the same conditions of preparing the sample for MALDI-MS analysis for each spot, and the reproducibility of the results of the "desalting/ concentration" procedure obtained from MALDI-MS analysis ( $r^2 = 0.9975$ ) (page 1769, right column, second paragraph). Zhang specifically indicates, "it is clear that sample preparation for MALDI analysis is a critical step in achieving high sensitivity and **reproducibility** for biological mixtures" (page 1771, left column). By the preparation of the sample he means removal of salts for highly salted analytes and *decreasing the volume of the sample*, with ~ 5 nL of the volume confirming high reproducibility of the experimental data, which comprise MALDI-MS spectra parameters.

### ***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459

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(1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 (a) are summarized as follows:

1. Determining the scope and contents of the prior art.
  2. Ascertaining the differences between the prior art and the claims at issue.
  3. Resolving the level of ordinary skill in the pertinent art.
  4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
9. **Claims 11-13, 29, 31-34, 40-42, 47, 51, 54-59, 61, 63-72, 82-85 and 87-94** are rejected under 35 U.S.C. 103 (a) as being unpatentable over Zhang in view of Nelson et al. (US 5,955,729).

Zhang does not specifically disclose a plurality of the vesicles forming an array, or pins with chambers delivering a solution (ink-jet applicators), and automation of the system.

Nelson discloses a surface plasmon resonance-mass spectrometry and an apparatus, which may comprise interaction analysis chip (IA chip). "In the case of IA sensor chips, a suitable matrix applicator is illustrated in FIG. 3. Matrix applicator (310) with guide pins (320) affixed thereto, is configured to accept the sensor chip affixed within a suitable chip holder (this aspect of the present invention is more fully discussed below in reference to FIG. 5). An appropriate MALDI matrix is applied to surfaces (330), (332), (334) and (336) of chip receptor (340), and the sensor chip holder (not shown) is positioned such that the individual interactive surfaces of the sensor chip (not shown) is brought in contact with surfaces (330), (332), (334) and (336). In this manner, the same or different MALDI matrix (or matrices) may be applied to the individual interactive surfaces of the IA sensor chip. *Alternatively, an ink-jet applicator may be employed, wherein the reservoir or "ink" of the applicator is the MALDI matrix. In this manner, the individual interactive layers of an IA sensor may be individually contacted with the*

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*MALDI matrix*" (col. 10, lines 5-23). Furthermore, "samples and reagents are delivered to the chip surface in regulated low volumes by a fully automated delivery flow system" (col. 8, lines 43-45).

It would have been obvious for anyone of ordinary skill in the art to modify Zhang's method for preparing MALDI-MS matrix by using plurality of vesicles in forms of capillaries, as disclosed by Zhang, or in form of pins (ink-jet applicators), with full automation of the fluid delivery, as disclosed by Nelson, because this is an obvious advantage regarding the speed and efficiency of the method of forming MALDI-MS substrate.

Although Zhang in view of Nelson do not specifically disclose TOF-MS analysis, it would have been obvious for anyone of ordinary skill in the art to use Zhang-Nelson's substrate for TOF-MS analysis, which also comprises desorbing the analyte from the matrix on the substrate.

10. **Claims 5, 45-46, 48-50 and 78** are rejected under 35 U.S.C. 103 (a) as being unpatentable over Zhang in view of Nelson, as applied to claims 11-13, 31-34, 40-43, 47, 51, 54-59, 64-72, 82-85 and 87-94 above, and further in view of Zhang et al. (J. Mass Spectrom.) (Zhang-2).

Zhang in view of Nelson do not specifically disclose preliminary disposition of the matrix material on the substrate with following ejection of the solution of the analyte into the same spots.

Zhang-2 teaches "continuous deposition on a matrix-precoated membrane target" for "capillary electrophoresis combined with MALDI-MS spectrometry".

It would have been obvious for anyone of ordinary skill in the art to slightly modify Zhang-Nelson's method by first placing matrix into the locations of the substrate, i.e. precoating the locations with the matrix the way taught by Zhang-2, and then depositing solution of the analyte into these locations, because Zhang-2 demonstrated the efficiency of such sequence in depositing the material. Although Zhang-2 does not teach the reverse disposition of the material on the substrate because of the specifics of his method, it would have been obvious for anyone of ordinary skill in the art to do so, because the main purpose of depositing a solution of the matrix and a solution of the analyte on the substrate is mixing the matrix and the analyte on the

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substrate, so the sequence of such deposition does not play much role if the right solvents are chosen by a routine experimentation.

11. **Claims 16-24** are rejected under 35 U.S.C. 103 (a) as being unpatentable over Zhang in view of Hancock et al. (US 5,716,825, IDS).

Zhang does not specifically disclose a material of the substrate or the nature of the wells of the multi-well sample holder.

Hancock discloses an integrated nucleic acid analysis system for MALDI-TOF MS, and describes in particular a thin film sample support, which is a substantially "planar manifold made of a non-conducting material that includes a microchannel and other necessary components of a miniturized sample preparation compartment, an interface to non-consumable parts, and an ionization surface for MALDI-TOF MS. Such a miniaturized device may be formed from a variety of materials (e. g., **silicon, glass, low cost polymers**) by techniques that are well known in the art (e.g., micromachining, chemical etching, laser ablation, and the like)" (col. 4, 11. 34-44). Hancock further describes a process wherein analyte is embedded in a solid or crystalline "matrix" of light-absorbing molecules (e. g., **nicotinic, sinapinic, or 3-hydroxypicolinic acid**) (col. 6, 11. 15-25). Hydrophobic and hydrophilic MALDI ionization surfaces, such as metals (**gold, copper, stainless steel**), glass, silica, nylon and other synthetic polymers, agarose and other carbohydrate polymers, and plastics are disclosed as surfaces for actively capturing analyte (col. 6, 11. 38-44). Other capture regions are disclosed, such as **surface of a bead, particle** or planar support treated with a bifunctional cross-linking reagent. "According to the practice of the present invention, a capture region may be formed in any microstructure surface in the sample preparation compartment by linking an analyte binding partner directly to the surface, and on MALDI ionization surfaces integrated with the preparation compartment. Alternatively, a capture region may be formed on the surfaces of beads, which can be chemically attached to the surface of the support, or magnetically attached by using magnetically responsive beads and applying a magnetic field to anchor the beads to the desired region of the support. Magnetically responsive beads and particles are well-known in the art and are commercially available from, for example, Dynal.RTM., Inc. (Lake Success, N.Y.) and Bangs Laboratories, Inc. (Carmel, Ind.)" (col. 7, 11. 30-43).

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It would have been obvious at the time the invention was made to a person having ordinary skill in the art to use any of the materials described by Hancock for Zhang's multi-well sample support (substrate), because Hancock gives more detailed description of the materials used for the preparation of samples for MALDI-MS analysis of DNA, including the support itself, while Zhang concentrates on the method of deposition of 5 nl of the material on this support.

12. **Claims 60 and 86** are rejected under 35 U.S.C. 103 (a) as being unpatentable over Zhang in view of Nelson, as applied to claims 11-13, 29, 31-34, 40-43, 47, 51, 54-59, 64-72, 82-85 and 87-94 above, and further in view of Hancock.

While Zhang in view of Nelson do not specifically disclose functionalized substrates, Hancock lists a plurality of possible materials for MALDI-MS substrates, including those recited in claims<sup>60 and</sup>86. It would have been obvious for anyone of ordinary skill in the art to use materials disclosed by Hancock in Zhang-Nelson's method, because these are convention materials for MALDI-MS substrates.

### *Response to Arguments*

13. Since the ground for rejections is revised ~~in~~ on the present Office action, the Applicants' arguments rendered to the previous Office action are moot in light of the new rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (703) 306-5906. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (703) 308-4037. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

Yelena G. Gakh  
11/15/03

